# Successive Osteosarcoma Relapses after the First Line O2006/Sarcome-09 Trial: What Can We Learn for Further Phase-II Trials?

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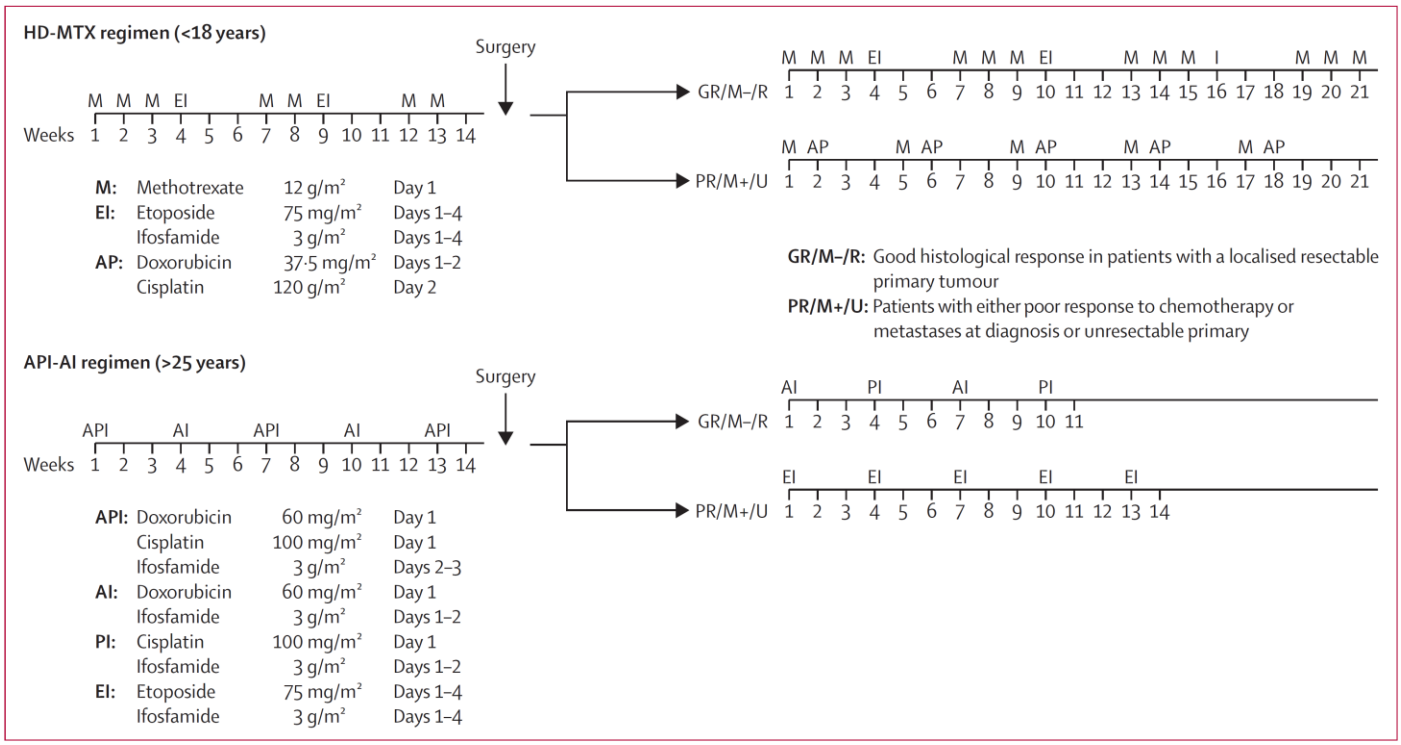
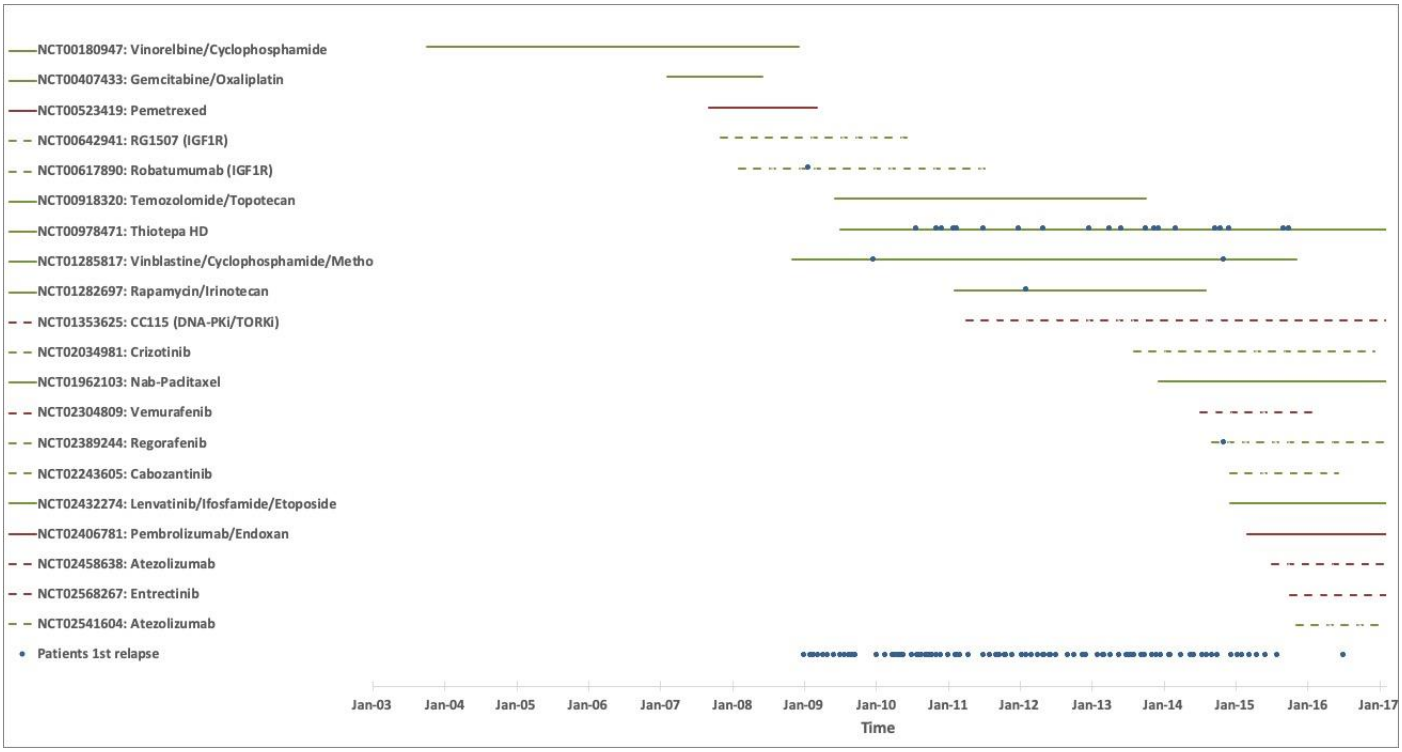
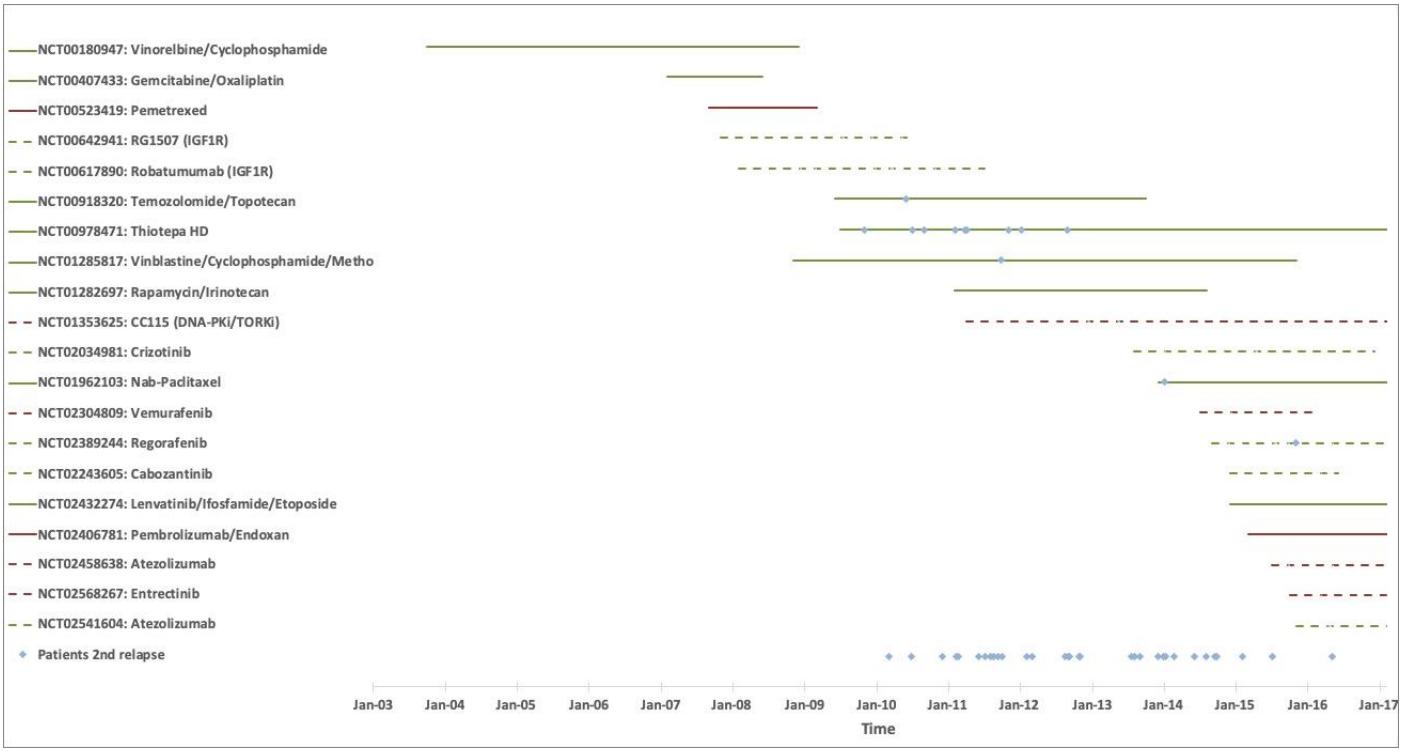



**Figure S1.** OS2006/Sarcome-09 Backbone chemotherapy scheme.




A




B

**Figure S2.** Active Phase-I and Phase-II trials for relapsed osteosarcoma in France between March 2007 and June 2016. **A**-Trials open for first osteosarcoma relapses. **B**-Trials open for second and subsequent osteosarcoma relapses. Plain line corresponds to trials with chemotherapy; dot line to trials without any chemotherapy agent; Green line to trials with paediatric population included; and red line to trials without paediatric population included (ie criterion ≥18 years).

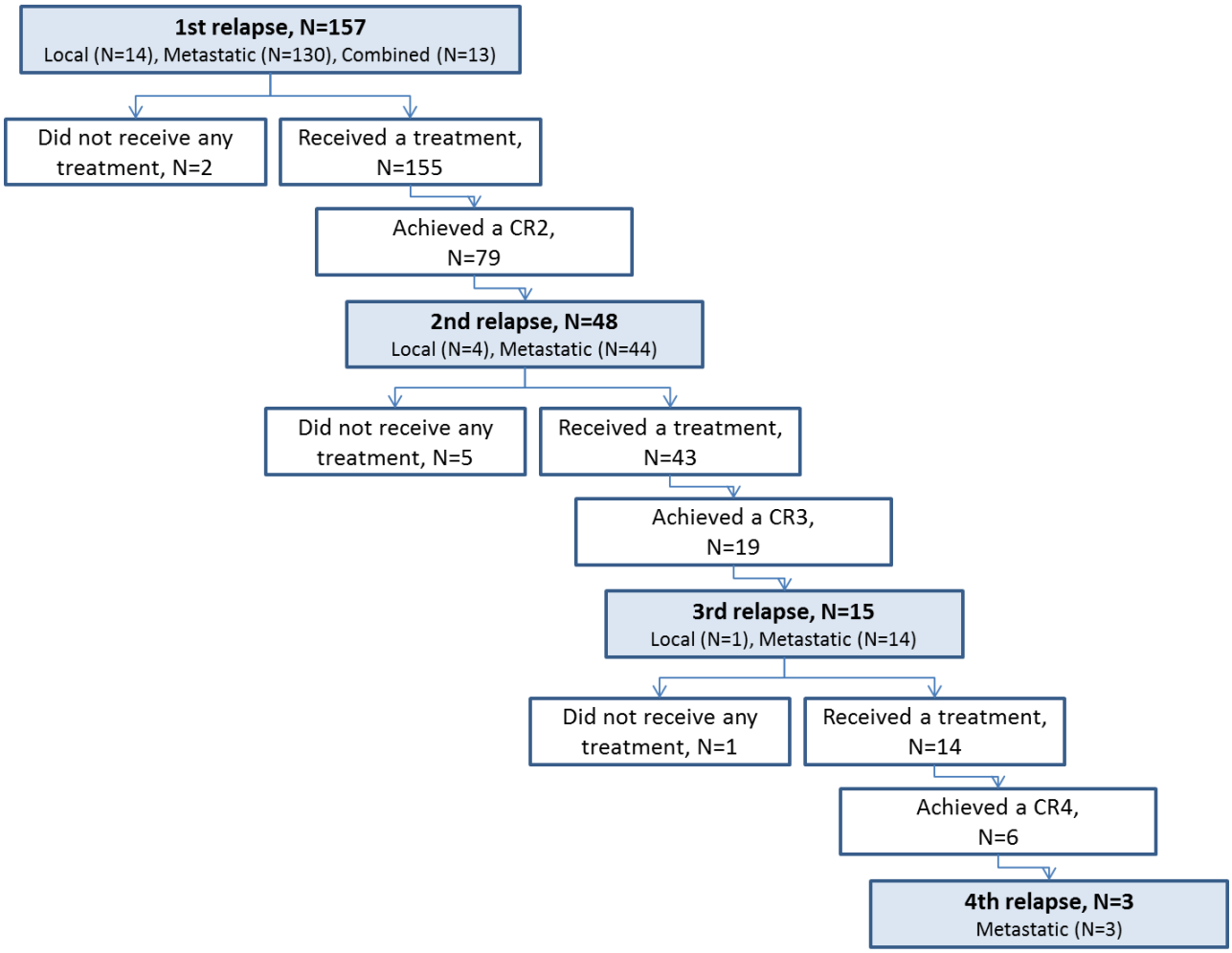



**Figure S3.** First and subsequent relapses of osteosarcoma.

**Table S1.** Open Trials for recurrent osteosarcoma in France between 04/2007 and 06/2016 (trials extracted from a previous paper 16)

| Publication Reference | Drug Tested | Diseases Included | Inclusion Criteria | | Inclusion | | Primary Endpoint | Response Evaluation Criteria | Trial | Randomization |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Age | Other | Start | End | | | | |
| **NCT00180947** | **Vinorelbine + Endoxan** | **Solid tumours** | **12m-25y** | **Relapse without standard therapy** | **oct-03** | dec-08 | 2 months Response rate | WHO | Phase II | No |
| **NCT00407433** | Gemcitabine + Oxaliplatin | Solid tumours | 6m-21y | Relapsed or refractory tumours | feb-07 | jun-08 | 2 months Response rate | WHO | Phase II | No |
| **NCT00523419** | Pemetrexed | Osteosarcoma | >18y | Already received first line chemotherapy | sept-07 | mar-09 | Best 1,5 months response rate | RECIST | Phase II | No |
| **NCT00642941** | Teprotumumab | Sarcoma | >2y | Recurrent or refractory sarcoma (osteosarcoma or other) | nov-07 | jun-10 | 6 months response rate | | Phase II | No |
| **NCT00617890** | Robatumumab | Osteosarcoma and Ewing's sarcoma | >4y | Relapse sarcoma operable or not | feb-08 | aug-11 | DCR (CR or PR) | RECIST or WHO | Phase II | No |
| **NCT00918320** | Temozolomide + Topotecan | Solid tumours | 6m – 20y | Relapsed or refractory tumours | jun-09 | oct-13 | 2 months Response rate | | Phase II | No |
| **NCT00978471** | Thiotepa HD | Osteosarcoma | 1-50ans | 1st relapse or 2nd relapse after surgery only; Surgery of all the sites of the relapse | jul-09 | dec-17 | 2 years OS | 0 | Phase II | Yes |
| **NCT01285817** | Celecoxib+Vinblastine + Cyclophosphamide + Methotrexate | Solid tumours | 4y-21y | Progression or Relapse; Refractory | nov-10 | nov-15 | PFS | ? | Phase II | No |
| **NCT01282697** | Rapamycin + Irinotecan | Solid tumours | 1y-21y | Relapsed or refractory tumours | feb-11 | aug-14 | Maximum tolerated dose | 0 | Phase I | No |
| **NCT01353625** | CC-115 (mTOR inhibitor) | Solid and Hematologic cancers | >18y | Progression or not tolerated standard therapy; Never treated with mTOR inhibitor | apr-11 | sept-18 | PD et PK | 0 | Phase I | No |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **NCT02034981** | Crizotinib | Hematologic and solid tumours | >1y | No standard therapy; One proven specific alterations among ALK, MET, RON, and ROS1 genes | aug-13 | dec-16 | 2 months Response rate | RECIST | Phase II | No |
| **NCT01962103** | Nab-Paclitaxel | Solid Tumours | 6m-24y | Solid tumours refractory or on relapse or without standard therapeutic | dec-13 | dec-18 | Best response rate | RECIST | Phase I/II | No |
| **NCT02304809** | Vemurafenib | Solid tumours or Hematologic cancers | >18y | Unresectable malignancy resistant or refractory; BRAF V600 mutation | jul-14 | feb-16 | 2 months Response rate | RECIST | Phase II | No |
| **NCT02389244** | Regorafenib | Ewing Sarcoma, Chondrosarcoma, Osteosarcoma, Chondroma | >10y | Progression disease; Metastatic disease not amenable to surgical resection | sept-14 | sept-19 | PFS | RECIST | Phase II | Yes |
| **NCT02243605** | Cabozantinib | Osteosarcoma and Ewing's sarcoma | >12y | Relapsed disease; Progressive disease | dec-14 | jun-16 | 6 months Non progression (CR, PR, SD) | RECIST | Phase II | No |
| **NCT02432274** | Lenvatinib +/- Cyclophosphamide and Etoposide | Solid tumours | 2y-25y | Relapsed or refractory tumour that has progressed | dec-14 | jun-18 | Objective response rate and 4 months PFS | RECIST | Phase I/II | No |
| **NCT02406781** | Pembrolizumab + Cyclophosphamide | Sarcoma | >18y | Advanced non resectable or metastatic disease; Progression | mar-15 | mar-17 | 6 months response rate | RECIST | Phase II | No |
| **NCT02458638** | Atezolizumab | Solid tumours | >18y | Progression disease | jul-15 | dec-20 | 4 months Non-progression rate (CR, PR, SD) | RECIST | Phase II | No |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **NCT02568267** | Entrectinib | Solid and hematologic cancers | >18y | NTRK1/2/3, ROS1, or ALK gene rearrangement; CNS involvement | oct-15 | oct-17 | Best response rate | RECIST | Phase II | No |
| **NCT02541604** | Atezolizumab | Solid tumours | <30y | Relapsed or refractory | nov-15 | janv-22 | PFS; Best response rate | RECIST | Phase I/II | No |

**Table S2.** Baseline patient and tumour characteristics and first-line treatment of the 157 patients with a relapse.

| Initial Characteristics | Number (%)<br>Median (min-max) |
|---|---|
| **Age at study entry in the OS2006/Sarcome-09 study, in years** | |
| Median (range) | 15.4 (6.4-50.4) |
| Less than 12 years, N (%) | 34 (21.7%) |
| 12-17 years, N (%) | 73 (46.5%) |
| 18-25 years, N (%) | 30 (19.1%) |
| >25 years, N (%) | 20 (12.7%) |
| **Primary tumour site** | |
| Trunk /head and neck, N (%) | 14 (8.9%) |
| Lower limb, N (%) | 117 (74.5%) |
| Upper limb, N (%) | 26 (16.6%) |
| **Metastasis at diagnosis** | 24 (15.3%) |
| Lung metastasis only, N (%) | 19 (12.1%) |
| Bone metastasis only, N (%) | 3 (1.9%) |
| Combined metastasis (Lung + other site), N (%) | 2 (1.3%) |
| **Type of centre for the first line treatment** | |
| Medical oncology department, N (%) | 52 (33.1%) |
| Paediatric centre, N (%) | 105 (66.9%) |
| **Chemotherapy as first-line treatment (OS2006 protocol)** | |
| Methotrexate-etoposide-ifosfamide, N (%) | 124 (79.0%) |
| API-AI, N (%) | 33 (21.0%) |
| **Treatment allocated by randomisation** | |
| No randomisation, N (%) | 58 (36.9%) |
| Without Zoledronate, N (%) | 45 (28.7%) |
| With Zoledronate, N (%) | 54 (34.4%) |
| **Surgery of the primary tumour** | |
| Conservative surgery, N (%) | 139 (88.5%) |
| Amputation, N (%) | 18 (11.5%) |
| **Histological response of primitive tumour** | |
| Good histological response (< 10% viable cells), N (%) | 89 (56.7%) |
| Poor histological response (≥ 10% viable cells), N (%) | 68 (43.3%) |

**Table S3.** Characteristics of the 39 patients with a unique lung nodule at first relapse, overall and according to treatment received at relapse.

| Patient and Tumour Characteristics | Overall<br>N = 39 | Surgery alone<br>N = 21 | Systemic Treatment<br>N = 18 | *p*-value |
|---|---|---|---|---|
| **Metastasis at diagnosis** | | | | 1.00 * |
| No Metastasis, N (%) | 30 (76.9%) | 16 (76.2%) | 14 (77.8%) | |
| Lung metastasis +/- other site, N (%) | 9 (23.1%) | 5 (23.8%) | 4 (22.2%) | |
| **Histological response of primitive tumour** | | | | 1.00 * |
| Good histological response, N (%) | 22 (56.4%) | 12 (57.1%) | 10 (55.6%) | |
| Poor histological response, N (%) | 17 (43.6%) | 9 (42.9%) | 8 (44.4%) | |
| **Type of centre** | | | | 0.07 * |
| Medical oncology department, N (%) | 10 (25.6%) | 8 (38.1%) | 2 (11.1%) | |
| Paediatric centre, N (%) | 29 (74.4%) | 13 (61.9%) | 16 (88.9%) | |
| **Age at relapse** (years) | | | | |
| Median (range) | 16.7 (8.4-43.6) | 17.4 (9.5-43.6) | 15.4 (8.4-25.7) | 0.18 ** |
| Less than 12 years, N (%) | 5 (12.8%) | 2 (9.5%) | 3 (16.7%) | |
| 12-17 years, N (%) | 20 (51.3%) | 9 (42.9%) | 11 (61.1%) | |
| 18-25 years, N (%) | 11 (28.2%) | 7 (33.3%) | 4 (22.2%) | |

| Patient and Tumour Characteristics | Overall N = 39 | Surgery alone N = 21 | Systemic Treatment N = 18 | *p*-value |
|---|---|---|---|---|
| >25 years, N (%) | 3 (7.7%) | 3 (14.3%) | 0 (0%) | |
| **Time interval from diagnosis to 1st relapse (years)** | | | | |
| Median (range) | 1.7 (0.9-5.7) | 1.9 (0.9-5.7) | 1.6 (1.2-3.6) | 0.75 ** |
| <1 year, N (%) | 1 (2.6%) | 1 (4.8%) | 0 (0%) | |
| >1 year, N (%) | 39 (97.4%) | 20 (95.2%) | 18 (100%) | |
| **Diameter of the nodule** | | | | |
| Median (range) | 15 (3-46) | 14 (4-43) | 16 (3-46) | 0.42 ** |
| <5 mm, N (%) | 3 (7.7%) | 1 (4.8%) | 2 (11.1%) | |
| 5-9mm, N (%) | 11 (28.2%) | 7 (33.3%) | 4 (22.2%) | |
| >=10mm, N (%) | 25 (64.1%) | 13 (61.9%) | 12 (66.7%) | |

* Fisher exact test; ** Wilcoxon test of the comparison of the distribution of the continuous variable.

**Table S4.** Characteristics of the subsequent relapses.

| Patient and Tumour Characteristics | First Relapse N = 157 | Second Relapse N = 48 | Third Relapse N = 15 |
|---|---|---|---|
| **Site of relapse** | | | |
| Local relapse, N (%) | 14 (8.9%) | 4 (8.3%) | 1 (6.7%) |
| Metastases only, N (%) | 130 (82.8%) | 44 (91.7%) | 14 (93.3%) |
| Combined, N (%) | 13 (8.3%) | 0 | 0 |
| **Treatment for relapse** | | | |
| None, N (%) | 2 (1.3%) | 5 (10.4%) | 1 (6.7%) |
| Systemic treatment, N (%) | 116 (73.9%) | 32 (66.7%) | 9 (60%) |
| Surgery, N (%) | 107 (68.2%) | 25 (52.1%) | 8 (53%) |
| Radiation therapy, N (%) | 17 (10.8%) | 8 (16.7%) | 1 (6.7%) |
| Radiofrequency ablation, N (%) | 2 (1.3%) | 2 (4.2%) | 1 (6.7%) |
| Other, N (%) | 1 (1.3%) | 0 (0%) | 1 (6.7%) |
| **Complete remission obtained**, N (%) | 79/155 (51.0%) | 19/43 (44.2%) | 6/14 (42.9%) |
| **Further relapse** | 48 | 15 | 3 |
| **Progression-Free Survival** | | | |
| 1-year | 41.8% | 27.1% | 36.6% |